REMARKS

Applicants acknowledge the Examiner's acceptance of the drawings filed on May 24, 2001.

The amendments to the specification now correctly denote trademarked items in full capitals and renumber the paragraphs to conform to the numbering of the published application . No new matter is introduced by way of the amendments to the specification.

Claims 95, 106, 108-121, 125, 128, 130, 131, and 145-163 are pending in the application.

The amendments to the claims find support in the specification as filed, for example, at page 5, lines 26-30 and page 6, lines 1-12 (paragraph 15); page 8, lines 1-13 (paragraph 20); page 18, lines 13-30 and page 19, lines 1-14 (paragraphs 56 and 57); page 25, lines 16-27 (paragraph 72); page 31, lines 8-13 (paragraph 86); page 34, lines 1-7 (paragraph 90); page 38, lines 5-8 (paragraph 99); and elsewhere in the specification. No new matter is added by way of the amendments and new claims.

Claims 95, 106, 108-121, 125, 128, 130, 131, 145, 146, 149-156, and 161-163 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 147-149, 153, 157 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Craig et al. (U.S. 6,656,696, hereafter "Craig"). Claims 150-152, 154-156, and 158-160 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Craig.

Applicants respectfully traverse these rejections to the claims.

The Rejections of Claims 95, 106, 108-121, 125, 128, 130, 131, 145, 146, 149-156, and 161-163 under 35 U.S.C. §112, Second Paragraph

Claims 95, 106, 108-121, 125, 128, 130, 131, 145, 146, 149-156, and 161-163 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 95 stands rejected under 35 U.S.C. §112,

second paragraph as being drawn to a polynucleotide encoding a chimeric phosphorylation indicator having an amino acid sequence of SEQ ID NO: 10 having Q69M, the Examiner alleging that the amino acid at position 69 is a leucine and not a methionine. Claims 106, 108-121, 125, 128, 130, 131, 145, 146, 149-156, and 161-163 are rejected as dependent on Claim 95.

As amended, Claim 95 notes that "the amino acid following the initiating methionine is assigned the '1' position in the numbering of said donor and acceptor amino acid sequences." This statement finds support in the specification at page 38, paragraph 99, in which several U.S. Patents discussing GFP spectral variants are incorporated by reference. For example, U.S. Patent 6,150,176 (which is incorporated by reference into the present application; see page 38, lines 8-10, paragraph 99) states that "The amino acids are numbered with the amino acid following the initiating methionine assigned to the '1' position" (column 5, lines 3-5). The numbering of the amino acid sequences disclosed in the present application follows this numbering scheme. For example, the amino acids of SEQ ID NO:6 and SEQ ID NO:10 at positions 206, 221, and 223 (as indicated at page 4, lines 20-23, paragraph 11) are A, L, and F according to this numbering scheme (*i.e.,* at positions 207, 222, and 224 of the sequence listing files with the application). As discussed by Tsien et al., Ann. Rev. Biochemistry 67:509-544, 1998, page 512, legend to Fig. 1, entitled "GFP sequences": "Numbering of amino acids and differences between EGFP and WT. The inserted Val is numbered 1a to maintain correspondence with the WT numbering." (This reference is incorporated by reference at page 19, lines 16-17, paragraph 58.)

When amino acid residues are numbered as indicated, the amino acid substitutions recited in the claims may be seen to be correct. Accordingly, Applicants respectfully submit that the rejections of Claims 95, 106, 108-121, 125, 128, 130, 131, 145, 146, 149-156, and 161-163 under 35 U.S.C. §112, second paragraph, are overcome.

The Rejection of Claim 108 Under 35 U.S.C. §112, Second Paragraph

Claim 108 stands rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for reciting A206K, L221K, F223R or L221K or F223R in either SEQ ID NO: 6 or 10, the Examiner alleging that, in these sequences, amino acid 206 is serine, and amino acid 223 is glutamic acid.

As discussed above, the amino acid residues are numbered with the amino acid following the initiating methionine being assigned the '1' position; thus, the amino acids at positions 206, 221, and 223 of SEQ ID NO: 6 or 10 are correctly identified in Claim 108. Accordingly, Applicants respectfully submit that the rejection of Claim 108 under 35 U.S.C. §112, second paragraph, is overcome.

The Rejections of Claims 147-148 and 153-160 Under 35 U.S.C. §112, Second Paragraph

Claims 147-148 and 153-160 stand rejected under 35 U.S.C. §112, second paragraph, as depending from canceled Claims 132 or 138.

As amended, Claim 147 is an independent claim, Claim 148 depends from Claim 147, and Claims 153 and 157 each depend from Claim 147 instead of Claim 132 and 138; and dependent Claims 154-156 and 158-160 properly depend from Claims 153 or 157. Accordingly, Applicants respectfully submit that the rejections to Claims 147-148 and 153-160 under 35 U.S.C. §112, second paragraph, are overcome.

The Rejections of Claims 150-152, 154-156 and 158-160 Under 35 U.S.C. §112, Second Paragraph

Claims 150-152, 154-156 and 158-160 stand rejected under 35 U.S.C. §112, second paragraph, the Examiner alleging that the phrases "different chimeric phosphorylation indicators," different phosphorylation domains," "different phosphorylatable peptides," "different phosphorylatable domains," "different donor molecules or acceptor molecules or both," and "different fluorescent proteins" are not clear.

As amended, the phrases that were objected to no longer appear in the claims. The claims now clearly state that the claimed kits comprise chimeric phosphorylation

indicators that differ from each other in their phosphoryatable domains, phosphorylatable peptides, phosphoaminoacid binding domains, non-oligomerizing fluorescent proteins, donor molecules, or acceptor molecules. Thus, the present claims particularly point out and distinctly claim the subject matter regarded as the inventions of these claims.

Accordingly, Applicants respectfully submit that the rejections to Claims 150-152, 154-156 and 158-160 under 35 U.S.C. §112, second paragraph, are overcome.

The Rejections of Claims 147-149, 153 and 157 Under 35 U.S.C. § 102(e)

Claims 147-149, 153 and 157 stand rejected under 35 U.S.C. §102(e) as allegedly anticipated by Craig.

Anticipation under 35 U.S.C. §102 requires that "every element of the claimed invention be identically shown in a single reference." (*In re Bond*, 910 F.2d 831,832 (Fed. Cir. 1990)).

However, Claims 147-149, 153 and 157 all require, among other elements, that the claimed polynucleotides encode a chimeric phosphorylation indicator comprising a phosphorylatable polypeptide and a non-oligomerizing fluorescent protein operatively linked to an expression control sequence. Craig nowhere discusses such a polynucleotide. For example, Craig nowhere discusses a polynucleotide encoding a chimeric phosphorylation indicator comprising a non-oligomerizing fluorescent protein; nor such a chimeric phosphorylation indicator comprising a non-oligomerizing fluorescent protein operatively linked to an expression control sequence; nor such a chimeric phosphorylation indicator comprising a phosphorylatable polypeptide and a non-oligomerizing fluorescent protein operatively linked to an expression control sequence.

Accordingly, failing to discuss polynucleotides having at least these elements of the claimed invention, Applicants respectfully submit that the rejections of Claims 147-149, 153 and 157 under 35 U.S.C. §102(e) are overcome.

The Rejections of Claims 150-152, 154-156, and 158-160 Under 35 U.S.C. §103(a)

Claims 150-152, 154-156, and 158-160 stand rejected under 35 U.S.C. §103(a) as allegedly obvious over Craig.

In order to establish a prima facie case of obviousness, there must be 1) some suggestion or motivation in the art or in the knowledge generally available to one of ordinary skill in the art, to modify or to combine the reference teachings; 2) there must be a reasonable expectation of success; and 3) the prior art references must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art, and not based on the applicant's disclosure. In re Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

As discussed above, Craig does not discuss polynucleotides having all the elements of the present claims. For example, Craig nowhere discusses chimeric phosphorylation indicators comprising a non-oligomerizing fluorescent protein, nor polynucleotides encoding a chimeric phosphorylation indicators comprising a non-oligomerizing fluorescent protein. In particular, Craig nowhere discusses kits including a plurality of such chimeric phosphorylation indicators, nor polynucleotides encoding such chimeric phosphorylation indicators, comprising non-oligomerizing fluorescent proteins. Craig also fails to discuss vectors comprising polynucleotides encoding chimeric phosphorylation indicators comprising non-oligomerizing fluorescent proteins.

Craig nowhere suggests non-oligomerizing fluorescent proteins, nor chimeric phosphorylation indicators comprising non-oligomerizing fluorescent proteins, nor polynucleotides encoding chimeric phosphorylation indicators comprising non-oligomerizing fluorescent proteins. Failing to suggest such proteins, polynucleotides, or chimeric phosphorylation indicators, Craig also fails to supply any motivation to provide such molecules, fails to supply any motivation to provide vectors comprising such polynucleotides, and fails to supply any motivation to provide kits containing such molecules.

Such motivation or suggestion is also lacking in the knowledge of one of ordinary skill in the art. For example, fluorescent resonance energy transfer (FRET) was known at the time of filing of the Craig application. Craig discusses FRET, stating that "[a]n important feature of the invention is that such measurements (*e.g.,* a shift in FRET) can be performed in real-time" (column 14, lines 42-44), and notes that "energy is transferred from an excited donor molecule to an acceptor molecule" in FRET (column 15, lines 26-27). Craig teaches that "the efficiency of this transfer is dependent upon the distance between the donor an [sic] acceptor molecules" (column 15, lines 27-29). Craig further teaches that "Since the rate of energy transfer is inversely proportional to the sixth power of the distance between the donor and acceptor, the energy transfer efficiency is extremely sensitive to distance changes." (column 15, lines 30-33). Thus, Craig teaches that FRET is an important feature, and that FRET is extremely sensitive to distance changes between donor and acceptor.

One of the elements of the present invention is a non-oligomerizing fluorescent protein. Not only does Craig fail to suggest a non-oligomerizing fluorescent protein as part of a phosphorylation indicator, Craig teaches away from such a suggestion. By teaching that FRET is an important feature and that FRET is extremely sensitive to distance changes between donor and acceptor, Craig teaches that a close association between donor and acceptor is important, and thus one of ordinary skill in the art reading Craig would expect, if presented with a suggestion based with hindsight on the present disclosure, that a non-oligmerizing fluorescent protein would be unsuitable. Accordingly, for at least this reason, Craig teaches away from the present invention.

Lacking at least these elements of the claimed invention, and lacking any suggestion of them or motivation to provide them, Craig also fails to provide any reasonable expectation of success for such proteins, polynucleotides, chimeric phosphorylation indicators, vectors or kits.

Accordingly, since the cited reference lacks elements of the present invention, does not provide any motivation to provide the claimed invention, and in fact, provides teaching that teaches away from the present invention, and fails

to provide any reasonable expectation of success, applicants respectfully submit that claims 150-152, 154-156, and 158-160 are not made obvious by Craig.

CONCLUSION

Applicants respectfully submit that all claim rejections and objections are overcome by the above arguments and amendments, and request reconsideration and allowance of Claims 95, 106, 108-121, 125, 128, 130, 131, and 145-163. An early indication of their allowance is earnestly requested. The Examiner is invited to contact the undersigned attorney at the telephone number indicated below should he find that there are any further issues outstanding.

Although no fees are believed to be due at this time, please charge any fees, including any fees for extension of time, or credit overpayment to Deposit Account No. **08-1641** referencing Attorney's Docket No. **39754-0891 CPC1CP1**.

Respectfully submitted,

Date: June 1, 2004

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